THE AMERICAN JOURNAL of MEDICINE®

Hereditary Angioedema with Normal C1 Inhibitor

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Angioedema is defined as ill-defined, localized, self-limiting facial, oral, laryngeal, genital, or peripheral swelling or abdominal pain in response to release of vasoactive mediators (bradykinin). It is more common in women, often associated with urticaria, and affects 15 percent of the population. Angioedema occurs in a variety of forms–idiopathic, allergic, hereditary or acquired, cytokine or autoimmune–thyroid-disease associated, physically or medication-induced angioedema (Figure 1).[1]

PRESENTATION

A 51-year-old Indian male with a history of positive purified protein derivative test (1979) *H. pylori*-associated chronic antral gastritis (2007) presented with recurrent swelling of the face for 5 years. Soon after a trip to India in 2002, he started having episodes of mid-abdominal pains and periorbital swelling. Swelling had progressed and involved the central face area. Symptoms were not affected by food, sun, scratching, pressure, cold or hot temperatures. Family history revealed that his mother had similar episodes involving lips and tongue. He denied any insect bites, allergy to medication or food, substance abuse, exposure to sexual disease or tuberculosis, fever, cough, hemoptysis, shortness of breath, choking, visual symptoms, nausea, diarrhea, weight loss, swelling of lips, tongue or extremities.

ASSESSMENT

On examination, he was afebrile. He had ill-defined, nonpitting edema of the eyelids and periorbital and central face areas (Figure 2). The rest of the examination was negative. Differential diagnosis included angioedema, cellulitis, and rosacea. The blood counts, hepatic and renal functions, prothrobin time, and urinalysis were negative. Chest x-ray revealed right apical old granulomatous disease. Absolute eosinophil count was normal (62, range 15-500) cells/μL. Complement studies demonstrated normal C1q (7.1, range 5-8.6) mg/dL; C3 (151, range 90-180) mg/dL; C4 (43, range 16-47) mg/dL; CH50 (54, normal 31-66) units per mL, and C1 inhibitor functional assay greater than 100 percent (above 68 percent is considered normal). Thyroid function

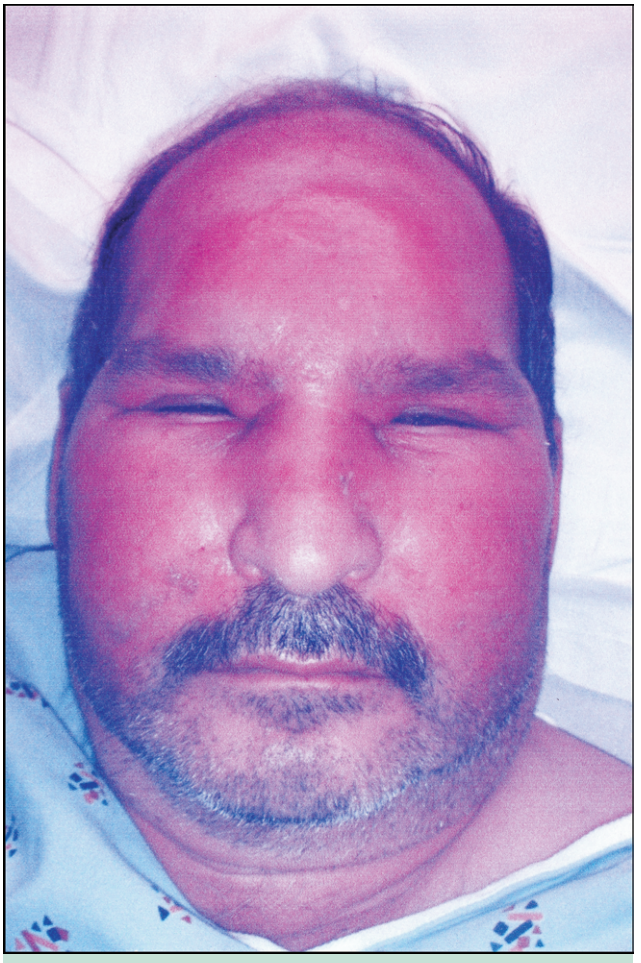

Figure 1 Acute attack of angioedema: note severe deep, diffuse swelling of face causing disfigurement. It occurred due to *ramipril*, an angiotensin-converting enzyme (ACE) inhibitor.

Conflict of interest: None; this manuscript is original, unpublished and not submitted elsewhere during the period of review. Both the authors have contributed to this paper.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.06.042

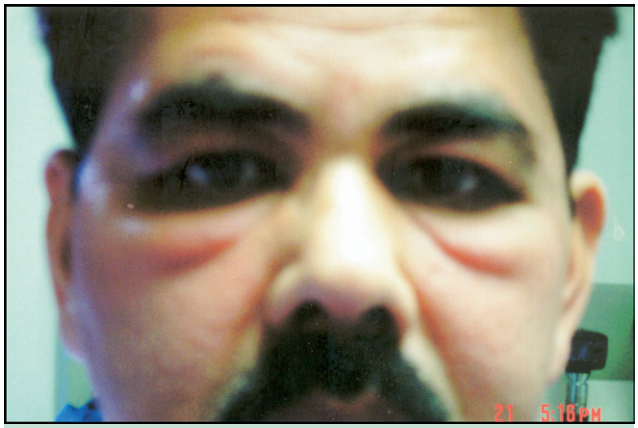

Figure 2 Hereditary angioedema: ill-defined, non-pitting facial edema.

tests, and CT scan of the abdomen and pelvis were unremarkable.

DIAGNOSIS

Hereditary angioedema is an "inherited" disorder characterized by episodic local subcutaneous and/or submucosal edema involving the upper respiratory and gastrointestinal tracts. Symptoms can start at any age and it is not associated with wheals (urticaria). Bradykinin is responsible for acute hereditary angioedema as evidenced by excess kallikrein in blister fluid, a decrease in prekallikrein/high molecular weight kininogen, and increased plasma bradykinin level.[2]

Three forms of hereditary angioedema have been described.[3] "Classic" hereditary angioedema types I and II are due to a mutation in C1-INH gene (SERPING 1), as a result less C1 INH (Hereditary angioedema type 1) or dysfunctional C1 INH is produced (Hereditary angioedema Type II). In both forms, deficiency of C1 inhibitor function leads to continuous activation of both C1 (with subsequent activation and consumption of early complement components and formation of C2b, a substrate for bradykinin formation) and kallikrein (with consequent bradykinin generation).

Hereditary angioedema type III or estrogen-sensitive hereditary angioedema or hereditary angioedema with normal C1 inhibitor or variant hereditary angioedema was first described in 2000.[4,5] It is chacterized by normal C1-INH lab tests, C4 and C1q during acute angioedema attack, a higher incidence in women in estrogen excess states (using birth control pills, adolescence, pregnancy), onset later in life, more frequent facial swelling (particularly tongue and lips), hemorrhages into skin, more disease-free intervals, less frequent symptoms, less frequent abdominal attacks, absence of erythema marginatum.[6]

In some estrogen-dependent hereditary angioedema type III patients, symptoms can be explained by missense mutation of coagulation factor XII gene (F12) located at chromosome 5q33-qter.[7] This is supported by the fact that estrogen upregulates transcription of the F12 gene, kinin production, and a decrease in angiotensin converting enzyme (ACE) induced degradation of bradykinin; increased factor XII amidolytic activity in female mutation carriers has been demonstrated.[8] This accentuated amidolytic activity results in formation of activated Hageman Factor, activated Factor XI and plasmin, the later cleaves C2b to form bradykinin. Moreover, activated Hageman Factor converts prekallikrin to kallikrein, which in turn converts activated Hageman Factor to prekallikrein activator (HFf), resulting in formation of kallikrein and bradykinin. Prekallikrein activator (HFf) (and plasmin), through activation of C1, forms C2b and then bradykinin.

C1 INH inhibits plasmin, kallikrein, prekallikrein activator (HFf), C1 activation, C2 and C4 degradation. C1 INH is normal in hereditary angioedema type III; defect might involve degradation of bradykinin by angiotensin-converting enzyme (ACE), aminopeptidase P, Carboxypeptidase N, and neutral endopeptidase. Hereditary angioedema type III was thought to be a disease only of females. Recent clinical studies have described males with hereditary angioedema type III and normal C1 inhibitor tests and disproved exclusive X-linked dominance inheritance.[6,9-11] They have mild, non- life threatening symptoms and can be referred to as having estrogen-independent hereditary angioedema type III.

TREATMENT

In hereditary angioedema attacks, airway must be protected immediately, followed by fresh frozen plasma during acute attacks. These attacks do not respond to antihistamines, corticosteroids or adrenaline. Estrogen, angiotensin receptor/ACE inhibitors and anti-androgens should be avoided and underlying infection (eg, H. *pylori*) must be treated.

Short term prophylaxis (eg, dental extraction) might involve fresh frozen plasma or danazol administration. Danazol (attenuated androgen) also is used for long-term prophylaxis of hereditary angioedema, especially in patients with a history of laryngeal edema, severe episodes more than once per month, or disability more than 5 days a month. Other alternative is antifibrinolytic agents (epsilon aminocaproic acid). C1 inhibitor concentrate products Berinert and Cinryze, Ecallantide (DX-88, kallikrein inhibitor), and icatibant (bradykinin-2 receptor antagonist) are undergoing clinical trials.

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